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In re Application of:

Duff, et al.

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For: *Diagnostics and Therapeutics for
Early-Onset Menopause*

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Art Unit: 1634

Examiner: Carla Myers

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Signed: Terrill Williams

Commissioner for Patents
Washington, D.C. 20231

Sir:

RESPONSE TO RESTRICTION REQUIREMENT

In response to the Restriction Requirement dated April 24, 2002, Applicants present the following claim amendments. Applicants traverse the restriction requirement, and the amendments are intended to expedite prosecution by obviating the restriction requirement. A clean set of claims is presented immediately below, and a set of claims showing amendments is presented at the end of the document. Applicants file herewith a request for a one month extension of time and a check for \$55.

IN THE CLAIMS:

Please cancel claims 2-4, 13-21 and 25-42. Please amend claims 1, 5-7 and 9, and add new claims 43 and 44.

A1
1. **(Amended)** A method for determining a subject's predisposition to early-onset menopause, comprising detecting at least one allele selected from the group consisting of: IL-1RN (+2018) allele 2; and IL-1RN (+2018) allele 1, wherein detection of the IL-1RN (+2018) allele 2 is predictive of the subject's predisposition to early-onset menopause.

2. - 4. **(Canceled)**

5. **(Amended)** The method of claim 1 wherein detecting said at least one allele comprises allele specific oligonucleotide hybridization.

A2
6. **(Amended)** The method of claim 1, wherein detecting said at least one allele comprises RFLP analysis.

7. **(Amended)** The method claim 1, wherein detecting said at least one allele comprises amplification of a nucleic acid.

8. The method of claim 7, wherein said amplification further comprises PCR.

A3
9. **(Amended)** The method of claim 7, wherein said amplification comprises using a first oligonucleotide that overlaps a second oligonucleotide, or a complement thereof, selected from the group consisting of:

5' CTA TCT GAG GAA CAA CCA ACT AGT AGC 3' (SEQ ID No.7); and

5' TAG GAC ATT GCA CCT AGG GTT TGT 3' (SEQ ID No.8)

10. The method of claim 9, wherein said first oligonucleotide comprises at least ten nucleotides of said second oligonucleotide.

11. A method for determining a subject's susceptibility to early-onset menopause comprising:

obtaining a nucleic acid sample from said subject; and,
genotyping said nucleic acid;

wherein detecting an allelic pattern from an IL-1 haplotype associated with early-onset menopause indicates an increased susceptibility to early-onset menopause.

12. The method of claim 11, wherein said haplotype associated with early-onset menopause comprises an allele selected from the group consisting of: IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2.

13. – 21. (Canceled)

22. A method of identifying an allelic pattern associated with early-onset menopause, said method comprising identifying a first allelic pattern that is in linkage disequilibrium with a second allelic pattern associated with early-onset menopause, wherein said first allelic pattern is associated with early-onset menopause.

23. The method of claim 22, wherein said first allelic pattern comprises alleles at a single polymorphic region within the IL-1 gene loci.

24. The method of claim 23, wherein said second allelic pattern is selected from the group consisting of IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2.

25. – 42. (Canceled)

A4
43. (New) A method for determining a subject's predisposition to early-onset menopause, comprising determining whether or not the subject carries a 44112332 haplotype, wherein determining that the subject carries the 44112332 haplotype indicates that the subject is predisposed to the early onset of menopause.

A4
44. (New) A method of claim 43, wherein determining whether or not the subject carries a 44112332 haplotype comprises detecting at least one allele selected from the group consisting of: IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2, or an allele in linkage disequilibrium with any of the above.

REMARKS:

Claims 2-4, 13-21 and 25-42 are canceled without prejudice and claims 1, 5-7 and 9 are amended. Claim cancellations and amendments are made solely to expedite prosecution and should not be interpreted as acquiescence to the restriction requirement. New claims 43 and 44 are added. Support for these new claims may be found throughout the specification and claims, such as, for example, in claims 1 and 11 as originally filed.

It is applicants belief that the amendments obviate the restriction requirement and will facilitate continued prosecution by removing any need for protracted argument relating to the nature of the restriction. Furthermore, Applicants believe that all of the claims now presented correspond to Group I of the original restriction requirement. Nonetheless, it should be understood that Applicants traverse the restriction on at least the grounds that a search for any one of the groups or alleles or nucleic acids would substantially overlap searches for the others, and that therefore restriction is unnecessary and inappropriate.

Furthermore, Applicants contest the requirement for election of a single nucleic acid from among those listed in claim 9. In amending the claims, Applicants have deleted all but two of the sequences in claim 9, SEQ ID Nos 7 and 8. SEQ ID Nos. 7 and 8 are examples of forward and reverse primers that may be used together to detect an IL-1RN (+2018) allele. While these nucleic acids may also be used separately, Applicants contend that they are sufficiently related that it is appropriate to examine them together.

If the Examiner is unpersuaded, then, in order to expedite prosecution, Applicants elect SEQ. ID. No. 7 for examination.

In addition, Applicants disagree with the requirement to elect a single allele where the effect of such an election is to select one allele of a locus and exclude an examination of other alleles of the same locus. For example, Applicants maintain that it is appropriate to examine claims related to IL-1RN (+2018) alleles 1 and 2 at the same time. Detection of an IL-1RN (+2018) allele 2 is useful for determining predisposition to early onset of menopause, and therefore detection of an IL-1RN (+2018) allele 1 is likewise useful because it is informative about the absence of the allele 2. Furthermore, a search with respect to allele 2 will surely be coextensive with a search for allele 1. Accordingly, Applicants urge the Examiner to examine each allele at a particular locus, and claim 1 is amended accordingly. If the Examiner disagrees, Applicants elect, with traverse, to have IL-1RN (+2018) allele 2 examined.

Applicants note that claims 11, 22 and 43 may, if the present restriction requirement were deemed proper, be considered linking claims with respect to dependent claims 12, 23 and 24, and 44, respectively. Applicants request that the Examiner follow a restriction practice as is typical for linking claims, as per 37 CFR 1.146. Accordingly, for the purposes of search only, Applicants elect the IL-1RN (+2018) allele 2, on the understanding that upon a finding of patentability of that one species, Applicants are entitled to an examination of other species.

In conclusion, Applicants request reconsideration and withdrawal of the present restriction requirement in view of these arguments and amendments. Should the Examiner disagree, then Applicants provisionally elect, with traverse, to have all of the claims pending upon entry of this amendment examined with respect to the IL-1RN (+2018) allele 2 and SEQ ID NO:7.

CLAIMS WITH AMENDMENTS SHOWN

1. **(Amended)** A method for determining a subject's predisposition to early-onset menopause, comprising detecting at least one allele selected from the group consisting of: IL-1RN (+2018) allele 2; and IL-1RN (+2018) allele 1, [IL-1RN (VNTR) allele 2; IL-1A

(222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2, or an allele in linkage disequilibrium with any of the above,] wherein detection of [said at least one allele] the IL-1RN (+2018) allele 2 is predictive of the subject's predisposition to early-onset menopause.

2. - 4. (Canceled)

5. (Amended) The method of claim 1 [any of claims 1-4] wherein detecting said at least one allele comprises allele specific oligonucleotide hybridization.

6. (Amended) The method of claim 1 [any of claims 1-4], wherein detecting said at least one allele comprises RFLP analysis.

7. (Amended) The method claim 1 [any of claims 1-4], wherein detecting said at least one allele comprises amplification of a nucleic acid.

8. The method of claim 7, wherein said amplification further comprises PCR.

9. (Amended) The method of claim 7, wherein said amplification comprises using a first oligonucleotide that overlaps a second oligonucleotide, or a complement thereof, selected from the group consisting of:

[5' CTC AGC AAC ACT CCT AT 3' (SEQ ID No. 5);

5' TCC TGG TCT GCA GGT AA 3' (SEQ ID No.6);]

5' CTA TCT GAG GAA CAA CCA ACT AGT AGC 3' (SEQ ID No.7);

5' TAG GAC ATT GCA CCT AGG GTT TGT 3' (SEQ ID No.8);

[5' CTC AGG TGT CCT CGA AGA AAT CAA A 3' (SEQ ID No.9);

5' GCT TTT TTG CTG TGA GTC CCG 3' (SEQ ID No.10);

5' AAG CTT GTT CTA CCA CCT GAA CTA GGC 3' (SEQ ID No.11);

5' TTA CAT ATG AGC CTT CCA TG 3' (SEQ ID No.12);

5' TGG CAT TGA TCT GGT TCA TC 3' (SEQ ID No.13);

5' GTT TAG GAA TCT TCC CAC TT 3' (SEQ ID No.14);

5' ATG GTT TTA GAA ATC ATC AAG CCT AGG GCA 3' (SEQ ID No.15);

5' AAT GAA AGG AGG GGA GGA TGA CAG AAA TGT 3' (SEQ ID No.16);

5' TTACGCAGATAAGAACCAGTTTGG 3' (SEQ ID No.17);

5' TTTCCTGGACGCTTGCTCACCAG 3' (SEQ ID No.18);

5' ATGTATAGAATTCCATTCCTG 3' (SEQ ID No.19);
5' TAAAATCAAGTGTTGATGTAG 3' (SEQ ID No.20);
5' GGGATTACAGGCGTGAGCCACCGCG 3' (SEQ ID No.21);
5' TTAGTATTGCTGGTAGTATTCATAT 3' (SEQ ID No.22);
5' GAGGCGTGAGAATCTCAAGA 3' (SEQ ID No.23);
5' GTGTCCTCAAGTGGATCTGG 3' (SEQ ID No.24);
5' GGGCAACAGAGCAATGTTTCT 3' (SEQ ID No.25); and
5' CAGTGTGTCAGTGTACTGTT 3' (SEQ ID No.26).]

10. The method of claim 9, wherein said first oligonucleotide comprises at least ten nucleotides of said second oligonucleotide.

11. A method for determining a subject's susceptibility to early-onset menopause comprising:

obtaining a nucleic acid sample from said subject; and,
genotyping said nucleic acid;

wherein detecting an allelic pattern from an IL-1 haplotype associated with early-onset menopause indicates an increased susceptibility to early-onset menopause.

12. The method of claim 11, wherein said haplotype associated with early-onset menopause comprises an allele selected from the group consisting of: IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2.

13. – 21. (Canceled)

22. A method of identifying an allelic pattern associated with early-onset menopause, said method comprising identifying a first allelic pattern that is in linkage disequilibrium with a second allelic pattern associated with early-onset menopause, wherein said first allelic pattern is associated with early-onset menopause.

23. The method of claim 22, wherein said first allelic pattern comprises alleles at a single polymorphic region within the IL-1 gene loci.

24. The method of claim 23, wherein said second allelic pattern is selected from the group consisting of IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2.

25. – 42. (Canceled)

43. (New) A method for determining a subject's predisposition to early-onset menopause, comprising determining whether or not the subject carries a 44112332 haplotype, wherein determining that the subject carries the 44112332 haplotype indicates that the subject is predisposed to the early onset of menopause.

44. (New) A method of claim 43, wherein determining whether or not the subject carries a 44112332 haplotype comprises detecting at least one allele selected from the group consisting of: IL-1RN (+2018) allele 2; IL-1RN (VNTR) allele 2; IL-1A (222/223) allele 4; IL-1A (gz5/gz6) allele 4; IL-1A (-889) allele 1; IL-1B (+3954) allele 1; IL-1B (-511) allele 2; gaat.p33330 allele 3; Y31 allele 3; IL-1RN exon 1ic (1812) allele 2; IL-1RN exon 1ic (1868) allele 2; IL-1RN exon 1ic (1887) allele 2; Pic (1731) allele 2; IL-1A (+4845) allele 1; IL-1B (+6912) allele 1; and IL-1B (-31) allele 2, or an allele in linkage disequilibrium with any of the above.

CONCLUSION:

Extension fees are filed herewith. If there are any additional fees in connection with the filing of this Response to Restriction Requirement, please charge the fees to our **Deposit Account No. 06-1448**. Please note that Applicants claim Small Entity Status, and any fees should be charged accordingly.

Respectfully submitted,



John D. Quisel
Reg. No. 47,874
Agent for Applicants

Patent Group
Foley, Hoag & Eliot LLP
One Post Office Square
Boston, MA 02109-2170
Tel.: (617) 832-1000
Fax: (617) 832-7000

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